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(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BLANCHARD, Steven, Gerard [US/US]; Glaxo Wellcome Inc., Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709 (US). COBB, Jeffery, Edmund [US/US]; Glaxo Wellcome Inc., Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709 (US). COLLINS, Jon, Loren [US/US]; Glaxo Wellcome Inc., Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709 (US). WILLSON, Timothy, Mark [GB/US]; Glaxo Wellcome Inc., Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709 (US).

(74) Agents: LEVY, David, J.; Glaxo Wellcome Inc., Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709–3398 (US) et al.

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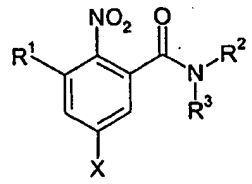

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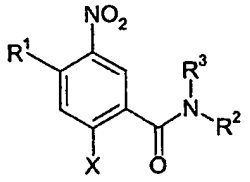

(IB)

(57) Abstract

The present invention discloses novel nuclear receptor ligands of formula (IA) or (IB). These compounds are useful for arylating a cysteine in a nuclear receptor.

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Nuclear Receptor Arylating Compounds

The present invention relates to compounds that bind to and arylate nuclear receptors. In another aspect, the present invention relates to methods for associating a particular disease or condition with a particular nuclear receptor.

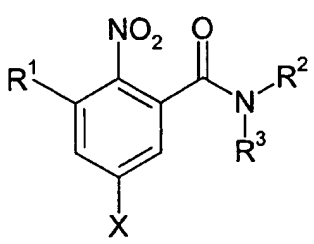
Nuclear receptors are transcription factors belonging to the steroid/retinoid receptor superfamily that are activated or deactivated by small lipophilic hormones. See, for example Mangelsdorf, D. J. et al., Cell, (1995), 83, 835-839. The Peroxisome Proliferator Activated Receptors (PPARs) are orphan members of the nuclear receptor superfamily. See, for example, Willson, T. M. and Wahli, W., Curr. Opin. Chem. Biol., (1997), Vol. 1, pp 235-241.

Three mammalian PPARs have been identified which are termed PPAR-alpha, PPAR-gamma, and PPAR-delta. PPARs regulate expression of target genes by binding to DNA response elements as heterodimers with the retinoid X receptor. These DNA response elements (PPRE) have been identified in the regulatory regions of a number of genes encoding proteins involved in lipid metabolism and energy balance. The biological role of the PPARs in the regulation of lipid metabolism and storage has been recently reviewed. See, for example, Spiegelman, B. M., Diabetes, (1998), Vol. 47, pp 507-514, Schoonjans, K., Martin, G., Staels, B., and Auwerx, J., Curr. Opin. Lipidol., (1997), Vol. 8, pp 159-166, and
Brun, R. P., Kim, J. B., Hu, E., and Spiegelman, B. M., Curr. Opin. Lipidol., (1997), Vol. 8, pp 212-218.

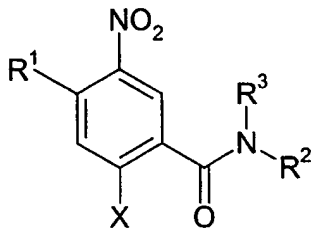
Essential dietary fatty acids and certain of their eicosanoid metabolites are naturally-occurring hormones for the PPAR receptors. These hormones can promote adipogenesis through activation of the PPAR-gamma receptor. See, for example, Kliewer, S. A., et al., Proc. Natl. Acad. Sci. USA, (1997), Vol. 94, pp 4318-4323, and Kliewer, S. A., et al., Cell, (1995), Vol. 83, pp 813-819. Molecules that inhibit the adipogenic effects of endogenous PPAR-gamma hormones may be useful in the treatment of diseases caused by

increased fat accumulation or lipid storage. See, for example, Tontonoz, P., Hu, E., and Spiegelman, B. M., Curr. Opin. Genet. Dev., (1995), Vol. 5, pp 571-576. Examples of these diseases are obesity, osteoporosis, and acne.

Briefly, in one aspect, the present invention discloses compounds of formula IA or IB,



IA



IB

where X is halogen;

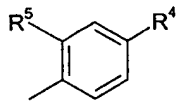
R^1 is H or $-OCH_3$;

R^2 is a hydrophobic organic group with molecular weight less than 500 Daltons; and

R^3 is H, C_{1-6}alkyl, or phenyl optionally substituted with 1 or 2 groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, and halogen. Preferably, the compounds of this invention are capable of binding to the ligand-binding domain of a nuclear receptor and arylating a cysteine residue of the receptor.

Preferably, X is Cl, F, or Br. Most preferably, X is Cl.

Preferably, R^2 is



or a $-C_{1-3}$alkenyl-adamantyl, where R^4 and R^5 are independently hydrogen or halogen. Most preferably, R^4 and R^5 are both H, both chloro, or one is H and one is iodo.

Preferably, R^3 is hydrogen, mono-substituted or un-substituted phenyl, or C_{1-3}alkyl. Most preferably, R^3 is H.

In another aspect, the present invention discloses a method of inhibiting the activity of a nuclear receptor by arylating a cysteine residue within the ligand-binding domain of said receptor.

In another aspect, the present invention discloses a method for associating a particular disease or condition with a particular nuclear receptor, for example PPARgamma. By "associating" is meant that the particular disease or condition can be treated by the administration of a compound that activates or deactivates the particular nuclear receptor.

In another aspect, the present invention provides a method for the treatment of a nuclear receptor mediated disease or condition by administration of a compound that activates or deactivates the particular nuclear receptor that was associated with said disease or condition using the method of this invention.

Preferred compounds of this invention are capable of binding to the ligand-binding domain of a nuclear receptor and arylating a cysteine residue of the receptor. Using well-known techniques compounds of formula IA or IB can be prepared, tested for binding to a particular receptor and analysed for arylation of the receptor. For example, a library of compounds of formula IA or IB can be prepared. The library can then be screened using a binding assay to identify members of the library that show affinity to a particular nuclear receptor, for example PPAR-gamma. Compounds that bind with a suitable apparent pKi, for example with an apparent pKi > 5, preferably > 7, would then be good candidates for arylating compounds. Arylation of cysteine residues within the nuclear receptor ligand-binding domain can be demonstrated by standard biochemical techniques, for example mass spectral analysis. Compounds that are shown to bind and to arylate, can be screened for selectivity using binding assays for other nuclear receptors, for example RXR. Generally this arylation of a cysteine in the ligand binding domain will block the functional activity of a nuclear receptor. This expected blocking could be confirmed using a cell-based reporter assay.

Arylating compounds that bind to a nuclear receptor and therefore block its functional activity in a cell line, cell culture, tissue, or whole animal can be used to associate the nuclear receptor with a mammalian disease. For example, arylating compounds that block PPAR-gamma activity inhibit adipogenesis, thereby suggesting that PPARgamma plays a role in adipogenesis. Although some nuclear receptors are associated with particular diseases or conditions, there may be more diseases or conditions that can be treated or prevented by a compound that activates or deactivates that receptor. Some nuclear receptors have no known utility. By using the associating methods of this invention, new disease-receptor associations can be discovered. Once these new associations are discovered, then new drugs for these diseases can be discovered by searching for compounds that activate or deactivate the receptor. Thus, the present invention provides new methods for drug discovery, and consequently new drugs for prevention and treatment of human diseases and conditions.

Suitable compounds of the present invention include:
N-phenyl-2-chloro-5-nitro-benzamide,
N-(2,4-dichlorophenyl)-2-chloro-5-nitro-benzamide,
N-(4-iodophenyl)-2-chloro-5-nitro-benzamide,
N-phenyl-5-chloro-3-methoxy-2-nitro-benzamide,
N-phenyl-2-fluoro-5-nitro-benzamide,
N-(1-tricyclo[3.3.1.13,7]dec-1-ylethyl)-2-chloro-5-nitro-benzamide, and
N-(2-ethoxyphenyl)-N-(6-bromo-1H-benz[de]isoquinoline-1,3(2H)-dioxo-eth-2-yl-)-2-chloro-5-nitro-benzamide.

A particularly preferred compound of the present invention is N-phenyl-2-chloro-5-nitro-benzamide.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms.

As used herein, "alkyl", "alkenyl", and similar terms and terms containing these terms, include straight-chain and branched-chain alkyl chains unless otherwise indicated.

The compounds of this invention can be prepared by standard organic chemistry as illustrated by the accompanying working examples. The following examples are set forth to illustrate the synthesis of some particular compounds of the present invention and to exemplify general processes. Accordingly, the following Examples section is in no way intended to limit the scope of the invention contemplated herein.

Examples

Example 1: N-phenyl-2-chloro-5-nitro-benzamide

To a stirred solution of 2-chloro-5-nitro-benzoyl chloride (5.03 g, 22.9 mmol) and triethylamine (3.51 mL, 25.1 mmol) in CH_2Cl_2 maintained under nitrogen at 0°C was added dropwise aniline (2.19 mL, 24.0 mmol). The resulting solution was stirred for 5 minutes at 0°C and then for 15 minutes at room temperature. This solution was then diluted with EtOAc (300 mL) and washed sequentially with 1.0 M HCl, water, 1.0 M $NaHCO_3$ and brine (100 mL each). The organic solution was then dried over MgSO4 and concentrated by rotary evaporation to give a light yellow solid (5.32 g) which was recrystallized from EtOAc to provide the title compound as a white solid (3.34 g, 53%): mp 155-156 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.63 (d, 1H, J=2.7), 8.28 (dd, 1H, J=2.7, 8.9), 7.81 (br s, 1H) 7.68-7.63 (m, 3H), 7.42 (t, 2H, J=7.9), 7.23 (t, 1H, J=7.5); MS (ES^-) *m/e* 275.1 $(M-H)^-$, Anal. Calcd. for $C_{13}H_9Cl_1N_2O_3$: C, 56.43; H, 3.28; N, 10.13; Found: C, 56.33; H, 3.30; N, 10.03.

Examples 2-5

In a similar manner to the preparation of Example 1, the following examples were prepared.

Example 2 N-(2,4-dichlorophenyl)-2-chloro-5-nitro-benzamide

Example 3 N-(4-iodophenyl)-2-chloro-5-nitro-benzamide

Example 4 N-phenyl-5-chloro-3-methoxy-2-nitro-benzamide

Example 5 N-phenyl-2-fluoro-5-nitro-benzamide

Binding assay

Test compounds were assayed for binding to the human PPAR-gamma receptor ligand binding domain by scintillation proximity assay (SPA) as described in Nichols, J. S., Parks, D. J., Consler, T. G., and Blanchard, S. G., Anal. Biochem., Vol. 257, pp.112-119, and Vol. 263, p 126 (1998),. Each of the above Examples 1-5 had an apparent pKi > 7 in this binding assay.

Binding to the PPAR-α and PPAR-δ ligand binding domains was determined in a similar manner using the previously described radioligands [^{3}H]-GW2331 (Kliewer, S.A. *et. al.*, and Lehmann, J.M. Proc. Natl. Acad Sci USA (1997) Vol.94 pp. 4318-4323) and [^{3}H]-GW2433 (Brown, P.J., Smith-Oliver, T. A., Charifson, P.S., Tomkinson, N.C.O., Fivush, A.M., Sternbach, D.D., Wade, L.E., Orband-Miller, L., Parks, D.J., Blanchard, S.G., Kliewer, S.A., Lehmann, J.A. and Willson, T.M. Chemistry and Biology (1997) Vol. **4**, pp.909-918) for PPAR-α and PPAR-δ, respectively.

The buffer used for the PPAR-γ and PPAR-α SPA was 50 mM KCl, 2 mM EDTA, 5 mM CHAPS, 0.1 mg/mL BSA, 10 mM DTT, and 50 mM Tris (2-amino-2-hydroxymethyl-1,3-propanediol) pH 8 (Buffer A). For the PPAR-δ SPA, the Tris was replaced with HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesufonic acid]) and the pH was 7 (Buffer B).

Analysis of the apparent binding affinity of the compound of Example 1, using standard scintillation proximity assays for PPARγ, PPARα, and PPARδ, showed that the compound is a selective ligand for PPARγ. Compared to its binding to PPARγ, the compound bound to PPARα and PPARδ with ~10-fold and ~600-fold lower affinity. Apparent pK_is of 8.48 ± 0.27 (K_i=3.3 nM; n=10), 7.49 ± 0.17 (K_i=32 nM; n=9), 5.69 ± 0.17 (K_i=2000 nM; n=3), were observed for binding to for PPARγ, PPARα, and PPARδ, respectively.

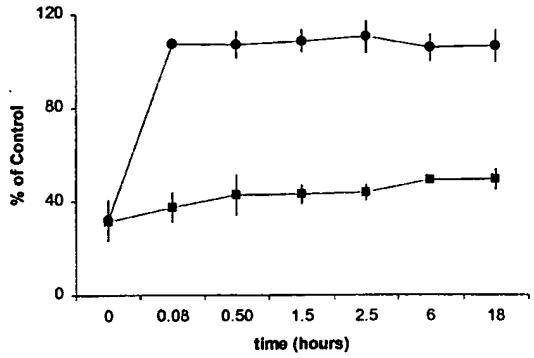
Cell-based report r assay

CV-1 cells were maintained in DME High Glucose medium (Irvine Scientific) supplemented with 10% fetal bovine serum and 2 mM Glutamine. Cells were split into D-MEM/F-12 medium (Gibco) supplemented with 10 % charcoal stripped fetal bovine serum for 3 d before harvesting. Cells were harvested into D-MEM/F-12 medium (Gibco) supplemented with 10 % charcoal stripped fetal bovine serum and counted. Cells were seeded at a density of 24,000 cells per well into 96-well plates and incubated overnight at 5% CO_2 and 37 °C. Cells were transfected for 6 to 20 hours based on the Lipofectamine protocol (Gibco) with the following amounts of DNA per well: 2 ng PSG5 GAL4-human PPAR-gamma, 8 ng UAS-tk-SPAP, 25 ng beta-gal, 45 ng pBluescript. See Lehmann, J. M. et al., J. Biol. Chem., (1995), Vol. 270, pp 12953-12956 and Brown, P. J. et al., Chem. Biol., (1997), Vol. 4, pp 909-918. Cells were incubated overnight at 5 % CO2 and 37 °C. Test compounds were solublized to 10 mM in DMSO. Test compounds were then serially diluted from 1e-5 M to 1e-10 M into D-MEM/ F-12 (Gibco) medium supplemented with 10% delipidated and charcoal stripped calf serum (Sigma) heat inactivated at 60 °C for 30 minutes, 2 mM Glutamine, and Pen-Strep. This medium into which the test compounds were diluted also contained 100 nM rosiglitazone. These test compound dilutions were added 100 microliters/well to the transfected cell plates after the transfection media were aspirated. DMSO controls and 1 micromolar rosiglitazone controls were added to each cell plate. Cells were incubated overnight at 5 % CO_2 and 37 °C. Cells were lysed with 25 microliters 0.5 % Triton X-100. Two daughter plates were made from each mother plate. One daughter received 200 microliters/well SPAP substrate (Sigma 104) and the other daughter received 200 microliters/well beta-gal substrate (Sigma N-1127). Once developed, cell plates were read at 405 nM. SPAP data were normalized to beta-gal, and % maximum inhibition of transactivation was calculated relative to the 1 micromolar rosiglitazone positive control. Each of the above Examples 1-5

had >50 % inhibition of transactivation by 100 nM rosiglitazone in this PPAR-gamma cell based reporter gene assay.

Blocking PPAR gamma Binding

PPARγ (in Buffer A) immobilised on SPA beads was incubated with 1 μM of the compound of Example 1 (■ in the graph below) or rosiglitazone (● in the graph below) for 1 hour. (Buffer A was used throughout this experiment.) This pretreating ligand was removed by two sequential steps of centrifugation followed by resuspension of the beads in fresh buffer. Recovery of binding was assessed by addition of [^{3}H]-rosiglitazone to an aliquot of the washed bead suspension followed by scintillation proximity assay to monitor the recovery of radioligand binding as a function of time. Biotinylated receptor immobilized on streptavidin-coated SPA beads was exposed either to vehicle, 1 μM the compound of Example 1, or to rosiglitazone. Following incubation for one hour, the pretreating ligand was removed from immobilized receptor and radioligand was added. Recovery of binding as a function of time was assessed by SPA. When PPARγ was treated with the compound of Example 1 in this manner, persistent inhibition of [^{3}H]-rosiglitazone binding to the receptor was observed. Little recovery of binding activity was observed at times up to 24 hours after removal of pretreating compound, suggesting that the inhibition was irreversible. In contrast, full receptor binding activity was recovered in parallel experiments where unlabeled rosiglitazone replaced the compound of Example 1 in the incubation. The recovery was rapid, reaching a maximum five minutes after dilution of the pretreating ligand. These results are summarised in the graph below.



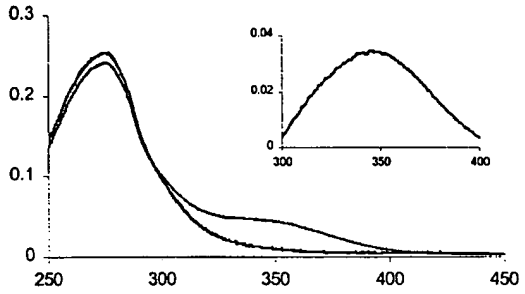
The standard conditions for the PPAR SPAs included 10 mM of the reducing agent dithiothreitol (DTT) in the assay buffers. The purpose of the DTT was two-fold. First, experiments had shown that maximal ligand binding was observed in the presence of reducing agent and that treatment of receptor with cysteine modifying reagents such as iodoacetamide inhibited radioligand binding. Therefore DTT reducing agent was added to increase ligand binding.

The second reason for use of DTT in the assay buffer was to act as a scavenger for nonspecific protein modifying reagents. As the concentration of DTT was more than six orders of magnitude above the concentration of receptor protein in the assay (~5 nM) the possibility of *nonspecific* receptor modification seemed unlikely.

The X-ray crystal structure of the PPARγ ligand binding domain (LBD) shows that the single cysteine residue in the LBD is located in helix 3, which defines part of the ligand binding site. See, R. T. Nolte et al, *Nature*, Vol. 395, pp 137-143 (1998). The following UV-Visible absorption study and LC-Mass Spec. Studies are designed to study the effect of compounds on this cysteine.

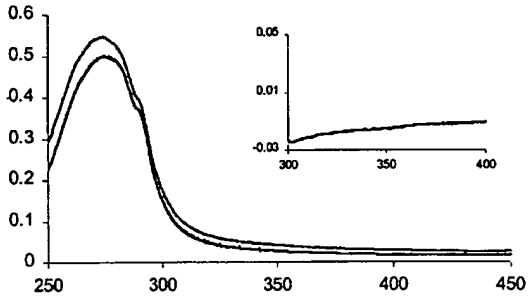
UV-Visibl Absorption

Covalent modification of reactive residues in proteins with nitro aryl halides such as dinitrofluorobenzene results in an increase in absorption at 330-360 nm. See, Means and Feeney, Chemical Modification of Proteins, Chapter 7, pp 118-123 (Holden-Day 1971). In the following experiments, spectra (in Buffer A) of the receptor protein and the compound of Example 1 were obtained separately. Backgrounds were subtracted and the two spectra were added together to give a composite spectrum for the unreacted sample (lower curve in each panel). The compound of Example 1 was then added to the receptor sample and a spectrum of the treated receptor was obtained (upper curves). As shown below, treatment of 5 μM PPARγ LBD with 5 μM (one equivalent) of the compound of Example 1 resulted in an increase in absorbance centered at 350 nm, consistent with covalent modification of the protein. The absorbance change was rapid; the maximal increase occurred in the time required to mix the sample and begin recording of the spectrum.



PPAR Gamma and Compound of Example 1

In contrast to the results observed with PPARgamma, as shown below, no change in absorbance was detected on treatment of 10 μM of the LBD of the unrelated Estrogen Receptor β with 10 μM of the compound of Example 1.



Estrogen Receptor and Compound of Example 1

LC-Mass Spec.

In order to directly demonstrate that treatment with the compound of Example 1 resulted in covalent modification of PPARγ, a sample of receptor was exposed to the compound and subjected to high-pressure liquid chromatography – electrospray ionization mass spectrometry. A second, untreated sample of receptor served as control. The treated sample showed an increase in molecular weight relative to the control that corresponded to the molecular weight of the compound of Example 1 minus HCl. Samples of the-modified PPARγ were subjected to digestion by the proteolytic enzyme Glu-C. Sequencing of the resulting peptides using mass spectrometry techniques confirmed Cys as the site of modification.

Adipocyte differentiation (adipogenesis) assay

C3H10T1/2 clone 8 murine fibroblasts (American Type Culture Collection) below passage 22 were maintained in Dulbecco's modified Eagle's medium (Life Technologies, Inc.) supplemented with 10 % fetal calf serum and 100 units/mL penicillin G and 100 microgram/mL streptomycin. One day after passage into 96-well microtiter plates (12.5 x 103 cells/cm^2), the cells were treated with 150 nM rosiglitazone plus 1 micromolar insulin and 1 micromolar 9-cis-retinoic acid (Sigma, St. Louis, Mo). Vehicle or test compounds, which had been solublized to 10 mM in DMSO and then serially diluted from 1e-5 M to 1e-10 M into medium, were added. After 7 days, cells

were lysed in 0.01% Digitonin (Sigma, St. Louis, Mo) and the lipogenic activity determined by measuring total triglycerides using a Glycerol-Triglyceride (GPO-Trinder) kit (337-B,Sigma, St. Louis, Mo). The mixture was incubated at 37 °C for 2 h and the absorbance read at 550 nm. The % maximum inhibition of lipogenesis was calculated relative to the vehicle treated cells. Example 1 had > 50 % inhibition of lipogenesis induced by 150 nM rosiglitazone in this adipocyte differentiation assay.

The following two examples were prepared and are useful for binding to and arylating CAR and LXR, respectively.

Example 6: N-(1-tricyclo[3.3.1.13,7]dec-1-ylethyl)-2-chloro-5-nitro-benzamide

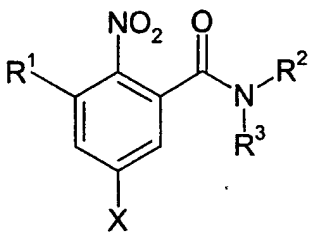
The title compound was prepared and is useful for binding to and arylating CAR. For information on CAR, see, for example, Forman, B. M. et al., Nature (1998), 395, 612-615.

Example 7: N-(2-ethoxyphenyl)-N-(6-bromo-1H-benz[de]isoquinoline-1,3(2H)-dioxo-eth-2-yl-)-2-chloro-5-nitro-benzamide

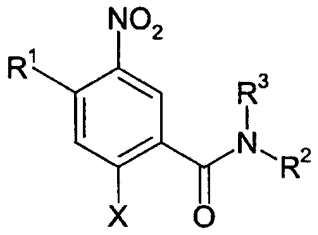
The title compound was prepared and is useful for binding to and arylating LXR. For information on LXR, see, for example, Peet, D. J. et al., Curr. Opin. Genet. Dev. (1998), 8, 571-575.

What is claimed is:

1. A compound of formula IA or IB,



IA



IB

where X is halogen;

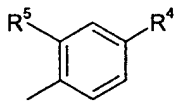
R^1 is H or $-OCH_3$;

R^2 is a hydrophobic organic group with molecular weight less than 500 Daltons; and

R^3 is H, C_{1-6}alkyl, or phenyl optionally substituted with 1 or 2 groups selected from C_{1-3}alkyl, C_{1-3}alkoxy, and halogen.

2. The compound of Claim 1 wherein X is Cl, F, or Br.

3. The compound of Claim 1 wherein R^2 is



or a $-C_{1-3}$alkenyl-adamantyl, where R^5 and R^4 are independently hydrogen or halogen.

4. The compound of Claim 3 wherein R^5 and R^4 are both are H, both chloro, or one is H and one is iodo.

5. The compound of Claim 1 wherein R^3 is hydrogen, mono-substituted or un-substituted phenyl, or C_{1-3}alkyl.

6. The compound of Claim 1 wherein R^3 is H.

7. The compound of Claim 1 wherein said compound is selected from the group consisting of
N-phenyl-2-chloro-5-nitro-benzamide,
N-(2,4-dichlorophenyl)-2-chloro-5-nitro-benzamide,
N-(4-iodophenyl)-2-chloro-5-nitro-benzamide,
N-phenyl-2-chloro-4-methoxy-5-nitro-benzamide,
N-phenyl-2-fluoro-5-nitro-benzamide,
N-(1-tricyclo[3.3.1.13,7]dec-1-ylethyl)-2-chloro-5-nitro-benzamide, and
N-(2-ethoxyphenyl)-N-(6-bromo-1H-benz[de]isoquinoline-1,3(2H)-dioxo-eth-2-yl-)-2-chloro-5-nitro-benzamide.

8. The compound of Claim 1 wherein said compound is N-phenyl-2-chloro-5-nitro-benzamide.

9. A method for associating a particular disease or condition with a particular nuclear receptor, comprising the step of arylating a cysteine in said receptor.

10. The method of Claim 9 wherein said cysteine is within the ligand-binding domain of said receptor.

11. The method of Claim 9 wherein said arylating comprises binding a compound of Claim 1 to said nuclear receptor.

12. The method of claim 9 wherein said receptor is PPARgamma, LXR, or CAR.

13. A method for inhibiting the activity of a nuclear receptor comprising the step of arylating a cysteine residue within the ligand-binding domain of said receptor.

14. The method of Claim 13 wherein said step of arylation comprises binding a compound of Claim 1 to said ligand-binding domain.

15. The method of Claim 14 wherein said receptor is PPARgamma, LXR, or CAR.

16. A method for the prevention or treatment of a particular disease or condition which has been associated with a particular nuclear receptor by the method of Claim 9, comprising administration of a therapeutically effective amount of a compound that activates or deactivates said receptor.

17. Use of a compound which activates or deactivates a particular nuclear receptor for the manufacture of a medicament for the treatment of a particular disease or condition which has been associated with a particular nuclear receptor by the method of Claim 9.

18. The method of Claim 16 or use according to claim 17 wherein said receptor is PPARgamma, LXR, or CAR.

INTERNATIONAL SEARCH REPORT

Int dional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C233/66 C07C233/65 C07C235/38 C07K14/705 A61P5/00
C07D221/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 310 760 A (WASHBURN WILLIAM N ET AL) 10 May 1994 (1994-05-10) column 8	1-8
X	NAGARAJAN K ET AL: "CONDENSED HETEROTRICYCLES*: AMINO & AMINOALKYLDIBENZUB,FU1,4OXAZEPIN-11(10H)-ONES" INDIAN JOURNAL OF CHEMISTRY,IN,JODHPUR, vol. 12, 1 March 1974 (1974-03-01), pages 236-246, XP000650379 page 5	1-6
P,X	WO 99 32477 A (SCHERING AG) 1 July 1999 (1999-07-01) abstract	1-6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2000	19/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rufet, J

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Int. Jonal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 97 19062 A (ALLERGAN INC) 29 May 1997 (1997-05-29) page 1 -page 4; claims 1-17	1,9
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 9-15, 17 partially

Present claims 9-15, 17 relate to an extremely large number of possible methods or uses. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the methods or uses claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. It is stressed that the expressions "particular disease" as well as "particular nuclear receptor" include a large number of possibilities, which render a complete search impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to methods associated to obesity disorders according to page 11 of the current application with the receptors PPAR, LXR and CAR.

Present claims 1, 17 relate to an extremely large number of possible compounds and their use. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to formulae IA or IB, wherein R2 has the definition given by claim 3. The compounds described by the examples have been also searched. It is stressed that the definition of R2 given in claim 1 contains merely thousands of possibilities, which render a complete search impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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